# General

## Guideline Title

Epithelial ovarian, fallopian tube, and primary peritoneal cancer.

## Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Tumour Team. Epithelial ovarian, fallopian tube, and primary peritoneal cancer. Edmonton (Alberta): CancerControl Alberta; 2013 Apr. 18 p. (Clinical practice guideline; no. GYNE-005). [121 references]

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Tumour Team. Epithelial ovarian, fallopian tube, and primary peritoneal cancer. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Apr. 16 p. (Clinical practice guideline; no. GYNE-005).

# Recommendations

## Major Recommendations

Staging of this cancer is based on the Fédération Internationale de Gynecologie et d'Obstétrique (FIGO) Staging. A detailed description of this staging system can be found in the Appendix of the original guideline document.

Key Points

1. Completely staged, early epithelial ovarian, fallopian tube, and primary peritoneal cancers are highly curable. As such, patients should be referred to a gynecologic oncologist for adequate staging, including sampling of para-aortic and pelvic lymph nodes, infracolic omentectomy, possible appendectomy and biopsy of suspicious peritoneal lesions, in addition to a thorough inspection and palpation of all peritoneal surfaces, and peritoneal washings.
2. Advanced epithelial ovarian, fallopian tube, and primary peritoneal cancers are best treated with optimal debulking surgery in conjunction with adjuvant therapy. As such, patients should be referred to a gynecologic oncologist.

Staging

- The gold standard for adequate staging includes inspection and palpation of all peritoneal surfaces, peritoneal washings, pelvic and para-aortic lymph node sampling, infracolic omentectomy, possible appendectomy, and biopsy of suspicious lesions and resection of adhesions adjacent to the primary tumour.
- Staging should be ideally performed by a gynecologic oncologist.

Early Stage: Stage I/IIA

Options include:

- Young patient: fertility preserving staging
- Older patient: total hysterectomy, bilateral salpingo-oophorectomy and staging
    - Stage IA/IB, Grade 1: Observation
    - Stage IA/IB, Grade 2
        - Observation depending on histologic type and individual case selection
        - Chemotherapy depending on histologic type and individual case selection
    - Stage IC/IIA, Grades 1–3
        - Chemotherapy with carboplatin and paclitaxel × 3 to 6 cycles dependent on histological type, grade, and individual case selection
- Clear cell carcinoma: Chemotherapy with carboplatin and paclitaxel × 3 to 6 cycles
- Papillary serous carcinoma:
    - Grade 1: Observation
    - Grade 2/3: Chemotherapy with carboplatin and paclitaxel × 6 cycles
- Endometrioid tumours:
    - Grade 1/2: Observation
    - Grade 3: Chemotherapy with carboplatin and paclitaxel × 3 to 6 cycles
- Mucinous tumours:
    - Grade 1/2: Observation
    - Grade 3: Chemotherapy with carboplatin and paclitaxel × 3 cycles
- Undifferentiated tumours: Chemotherapy with carboplatin and paclitaxel × 6 cycles
- If incomplete staging, consider:
    - Completion of surgical staging if medically fit patient +/- chemotherapy as indicated
    - OR chemotherapy

Intermediate Stage: Stage IIB/IIC

Options include:

- Medically unfit patients and/or patients who cannot be optimally debulked:
    - Chemotherapy × 6 cycles
    - OR chemotherapy × 3 to 6 cycles depending on individual case selection followed by interval debulking surgery (IDS):
        - If microscopic residual disease at IDS, then chemotherapy × 3 cycles
        - If macroscopic residual disease at IDS, then chemotherapy × 3 to 6 cycles
        - Note: total chemotherapy would not normally exceed 9 cycles.
- Patients undergoing primary debulking surgery:
    - Optimal debulking is ideally defined as microscopic residual disease or, at most, macroscopic residual disease <1 cm.
    - Debulking would include total hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and maximum reduction of pelvic tumour.
    - Debulking is typically followed by chemotherapy x 6 cycles depending on individual case selection.
- If incomplete primary debulking surgery, consider:
    - Completion of surgical debulking if medically fit patient +/- chemotherapy as indicated
    - OR chemotherapy.

Advanced Stage: Stage III/IV

Options include:

- Medically unfit patients and/or patients who cannot be optimally debulked:
    - Chemotherapy × 6 cycles
    - OR chemotherapy × 3 to 6 cycles depending on individual case selection followed by IDS:
        - If microscopic residual disease at IDS, then chemotherapy × 3 cycles
        - If macroscopic residual disease at IDS, then chemotherapy × 3 to 6 cycles
        - Note: total chemotherapy would not normally exceed 9 cycles.

- Patients undergoing primary debulking surgery:
  - Optimal debulking is ideally defined as microscopic residual disease or, at most, macroscopic residual disease <1 cm.
  - Debulking would include total hysterectomy, bilateral salpingo-oophorectomy, omentectomy and maximum reduction of pelvic tumour +/- upper abdominal tumour, including possible resection of involved bowel, lymph nodes, retroperitoneal masses, spleen, etc.
  - Debulking is typically followed by chemotherapy x 6 cycles depending on individual case selection.
- If incomplete primary debulking surgery, consider:
  - Completion of surgical debulking if medically fit patient +/- chemotherapy as indicated
  - OR chemotherapy

Chemotherapy

*Preferred* options include:

- Dose dense intravenous (IV) chemotherapy regimen: carboplatin (area under the curve [AUC] 5 to 6 IV on day 1) + paclitaxel (80 mg/m$^2$ IV on days 1, 8, 15), q 3 weeks × 6 cycles
- Intraperitoneal (IP) chemotherapy regimen: day 1: cisplatin (75 mg/m$^2$ IP) + paclitaxel (135 mg/m$^2$ IV); day 8: paclitaxel (60 mg/m$^2$ IP), q 3 weeks × 6 cycles
- Clinical trials

*Other* option:

- IV chemotherapy regimen: carboplatin (AUC 5 to 6 IV) + paclitaxel (175 mg/m$^2$ IV), q 3 weeks × 6 cycles

*Modifications*:

- If hypersensitivity to paclitaxel, substitute with docetaxel (75 mg/m$^2$ IV).
- If significant toxicity develops, or in medically unfit patients, consider single agent carboplatin (AUC 5 or 6 IV) and/or dose reduction at the discretion of the oncologist
- If hypersensitivity to platinum, consider desensitization protocol.
- Note: The use of Abraxane (nab-paclitaxel) in this setting is not funded in Alberta at the present time.

Radiotherapy

Consider in select cases to improve local control, at the discretion of the radiation oncologist.

Recurrent Disease

Options include:

- Clinical trials
- Carboplatin +/- paclitaxel
- Carboplatin/liposomal doxorubicin
- Liposomal doxorubicin
- Topotecan
- Cisplatin +/- liposomal doxorubicin
- Also consider: docetaxel, etoposide (oral), gemcitabine, paclitaxel, tamoxifen, or melphalan
- Consider cytoreductive surgery if clinically low volume of focal recurrence followed by clinical trial or platinum-based chemotherapy (below)

Recurrence >12 months: consider cytoreductive surgery followed typically by carboplatin/paclitaxel chemotherapy.

Follow-up and Surveillance

Follow-up should include a complete history and a pelvic examination as follows:

- Years 1 and 2: q 3 to 6 months
- Years 3 through 5: q 6 to 12 months

CA-125 blood tests and radiographic scanning have not been proven to be beneficial and are therefore not recommended for routine follow-up.

## Clinical Algorithm(s)

An algorithm titled "Algorithm for the Diagnosis & Management of Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer (GYNE-005)" is provided on the Alberta Health Services Web site .

# Scope

## Disease/Condition(s)

- Epithelial ovarian cancer
- Fallopian tube cancer
- Primary peritoneal cancer

## Guideline Category

Evaluation

Management

Treatment

## Clinical Specialty

Obstetrics and Gynecology

Oncology

Radiation Oncology

Surgery

## Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

## Guideline Objective(s)

To evaluate management and treatment strategies for women with epithelial ovarian, fallopian tube, or primary peritoneal cancer

## Target Population

Adults over the age of 18 years with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer

Note: Different principles may apply to pediatric patients.

## Interventions and Practices Considered

Evaluation/Staging

1. Inspection and palpation of all peritoneal surfaces
2. Peritoneal washings
3. Pelvic and para-aortic lymph node sampling
4. Infracolic omentectomy
5. Possible appendectomy
6. Biopsy of suspicious lesions
7. Resection of adhesions adjacent to the primary tumour

Treatment/Management

1. Referral to a gynecologic oncologist
2. Young patient: fertility preserving staging
3. Older patient: total hysterectomy, bilateral salpingo-oophorectomy and staging
4. Observation
5. Intravenous or intraperitoneal chemotherapy (carboplatin or cisplatin + paclitaxel or docetaxel)
6. Chemotherapy with interval debulking surgery (IDS)
7. Primary debulking surgery followed by chemotherapy
8. Radiotherapy
9. Treatment of recurrent disease (chemotherapy, cytoreductive surgery)
10. Follow-up (complete history and a pelvic examination)

Note: CA-125 tests and radiographic scanning were considered but not recommended for routine follow-up.

## Major Outcomes Considered

- Survival (overall, 5-year, progression free)
- Morbidity
- Adverse effects of treatment
- Overall response rate

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

1. What is considered optimal debulking for advanced stage disease?
2. What is the optimal adjuvant chemotherapy (if any) for early-stage disease?
3. What should be chosen for first line chemotherapy for the treatment of advanced stage disease?
4. What role (if any) does intraperitoneal chemotherapy play in adjuvant treatment for patients with advanced stage disease? If so, who should receive this treatment and what regimen(s) should be used?

5. What role (if any) does neoadjuvant chemotherapy play for patients with advanced stage disease? Which treatment regimen(s) should be used?
6. What is considered optimal timing/regimen for interval debulking surgery and adjuvant chemotherapy afterwards?
7. What is (are) the best choice(s) of second-line treatment(s) for recurrent disease?
8. What is the role of secondary cytoreduction after a recurrence?
9. What additional therapy can be administered for recurrent disease after failure of second and third-line treatment?
10. What is the optimal treatment for disease that recurs between 6 and 12 months of treatment?
11. What is the optimal monitoring regimen (if any) during treatment to measure response?
12. What is the optimal surveillance for cancer recurrence following treatment and clinical remission?
13. How should clear cell carcinoma be managed?
14. What are the indications for docetaxel to be administered and what is the optimal treatment regimen?

Search Strategy

Entries to the Medline, EMBASE, and Cochrane databases and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms included: (ovary AND cancer or neoplasm AND epithelial OR epithelial ovarian cancer) AND chemotherapy or adjuvant chemotherapy or intraperitoneal chemotherapy or taxotere or platinum chemotherapy or optimal debulking or second line treatment or second line chemotherapy or salvage treatment or salvage therapy or third line treatment or third line chemotherapy or chemotherapy resistant, with limits of human studies in females only in the English language.

Guidelines reviewed include the following: the National Comprehensive Cancer Network (NCCN) guidelines (2013), the European Society for Medical Oncology (ESMO) guidelines (2013), the BC Cancer Agency (BCCA) guidelines (2006), Cancer Care Ontario (CCO) Program in Evidence-Based Care guidelines (2004–2011) and the National Health and Medical Research Council (Australia) and the Tom Baker Cancer Centre guidelines.

The guideline was originally developed in 2011 and then updated in 2012 and 2013. The literature was reviewed prior to each update, using the search strategy described above.

## Number of Source Documents

The 2012 and 2013 reviews included a total of 35 studies and 8 studies, respectively.

## Methods Used to Assess the Quality and Strength of the Evidence

Not stated

## Rating Scheme for the Strength of the Evidence

Not applicable

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org ) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Following a review of the evidence by the Alberta Provincial Gynecologic Oncology Team, no major changes were made to the recommendations, with the exception of classifying dose-dense and intraperitoneal chemotherapy as preferred options for chemotherapy. The guideline was otherwise reaffirmed.

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

## Method of Guideline Validation

Internal Peer Review

## Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized.

Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Appropriate management of epithelial ovarian, fallopian tube, and primary peritoneal cancers to improve survival, preserve fertility, and minimize morbidity

## Potential Harms

- Toxicity of treatment
- In one reported phase III randomized controlled trial comparing patupilone with pegylated liposomal doxorubicin (PLD), the most common adverse events were diarrhea (85.3%) and peripheral neuropathy (39.3%) for patupilone and mucositis/stomatitis (43%) and hand-foot syndrome (41.8%) for PLD.

# Qualifying Statements

## Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

# Implementation of the Guideline

## Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

## Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Living with Illness

## IOM Domain

Effectiveness

# Identifying Information and Availability

## Bibliographic Source(s)

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## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2010 Jul (revised 2013 Apr)

## Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

## Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

## Guideline Committee

Alberta Provincial Gynecologic Oncology Tumour Team

## Composition of Group That Authored the Guideline

Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists.

## Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Tumour Team. Epithelial ovarian, fallopian tube, and primary peritoneal cancer. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Apr. 16 p. (Clinical practice guideline; no. GYNE-005).

## Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

## Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on February 10, 2012. The information was verified by the guideline developer on March 30, 2012. This summary was updated by ECRI Institute on December 31, 2012. The updated information was verified by the guideline developer on February 5, 2013. This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on May 22, 2014. This summary was updated by ECRI Institute on July 18, 2014 following the U.S. Food and Drug Administration advisory on Docetaxel.

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